REMARKS

Claims 1-115 were pending in the application. Claims 1-29, 35-73, 76-88 and 95-115 and 97-116 were withdrawn from consideration as directed to non-elected inventions.[1] Claims 30, 32, 33, and 35 have been amended. Claims 31, 34, 74 and 75 have been canceled without prejudice to presentation in related applications.

Claim 30 has been amended to remove dependency from a non-elected claim. Claim 32 has been amended to update its dependency and to add a specific level of homology. Claim 33 has been amended to make it independent, remove reference to non-elected sequences, and to recite a specific level of homology. The dependency of claim 35 has been amended. Support for the claim amendments can be found throughout the specification as filed.

The title has been amended as requested by the Office. The specification has been amended to remove embedded hyperlinks.

Applicants note that claims 89-94, although drawn to "ion-x polypeptides", are directed to non-elected species (SEQ ID NO:22 and SEQ ID NO:38). Accordingly, Applicants presume that claims 89-94 shall be withdrawn from consideration.

No new matter has been added.

Upon entry of this amendment, claims 30, 32, 33, and 35 will be pending.

Specification

The Office alleges that the title is not descriptive. Applicants respectfully disagree. However, in order to further prosecution, Applicants have amended the title.

The specification was objected to for allegedly improper hyperlink usage. Applicants have amended the specification to remove embedded hyperlinks.

In view of the foregoing, Applicants respectfully request that the objections to the specification be withdrawn.

[1] Applicants note that claim 35 was erroneously included in the list of withdrawn claims. As set forth in the Office Action dated October 7, 2002 (paper number 11), claim 35 is part of Group II, "drawn to an ion-x polypeptide."

Objections

Claims 30-89 stand objected for depending from non-elected claims. Claim 30 has been amended so that it no longer depends on a withdrawn claim. As discussed above, claim 89 recites non-elected species; Applicants presume that claim 89 will be withdrawn from consideration.

In view of the foregoing, Applicants respectfully request that the objections be withdrawn.

Rejection under 35 U.S.C. §101

Claims 30-35, 74, 75 and 89-94 stand rejected under 35 U.S.C. § 101 because the claimed invention allegedly "lacks a credible, specific and substantial utility or a well-established utility." (Office Action, page 5). Applicants respectfully disagree.

The Office alleges that the utilities asserted for the claimed invention are either "credible, but not specific or substantial" (for the production of antibodies; to make hybridization probes and primers to detect nucleic acid molecules that encode the polypeptide of SEQ ID NO:20 and to localize gene expression in tissue samples; to produce a variant or chimeric polypeptide; in the creation of transgenic animals; to detect pharmacogenomically-relevant polymorphisms in individuals; to search for drugs as ligands or antagonists of the claimed polypeptide; and for gene therapy), or are "credible and specific, but not substantial." (Office Action, pages 5-8). Applicants disagree.

Utility Examination Guidelines

The Utility Examination Guidelines require a claimed invention have a specific, substantial and credible asserted utility, or, alternatively a well-established utility. As Applicants have asserted utilities that are specific, substantial and credible, and well established, the Utility Requirement has been satisfied. Applicants therefore respectfully request the withdrawal of the rejection under 35 U.S.C. § 101.

Specific Utility

The Utility Examination Guidelines require a claimed invention to have a utility that is specific to the subject matter claimed (a "specific utility"). The present application recites, for example, that the claimed invention can be used, *inter alia*, to identify ligands and/or protein binding partners. As acknowledged by the Office, the presently claimed invention can be used for many different purposes. For example, the polypeptides of the present invention can be used for the production of antibodies; to make hybridization probes and primers to detect nucleic acid molecules that encode the polypeptide of SEQ ID NO:20 and to localize gene expression in tissue samples; to produce a variant or chimeric polypeptide; to create transgenic animals; to detect pharmacogenomically-relevant polymorphisms in individuals; to search for drugs as ligands or antagonists of the claimed polypeptide; and for gene therapy, among others. Thus, there is no question that Applicants have asserted at least one specific utility and, in fact, have provided numerous specific utilities for the polypeptides of the present invention.

Additionally, the Office appears to be under the assumption that ***absolute*** certainty is required for a polynucleotide or polypeptide to have a specific utility. The Office states, "There is little doubt that, after complete characterization, this protein will probably be found to have a patentable utility. This further characterization, however, is part of the act of invention and, until it has been undertaken, Applicant's' claimed invention is incomplete." (Office Action, page 5).

The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability as the Supreme Court stated applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner v. Manson*, 383 U.S. at 532. Although, there may be numerous inventions that may arise from the present application, this standard does not justify the Office's stance that the present invention lacks a specific utility. Thus, Applicants have complied with the specific utility requirement.

The Training Materials associated with the Utility Examination guidelines address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities

which meet the statutory requirements, and "general" utilities which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials further distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," or unique (Training Materials at p.52) as compared to the "broad class of invention." Applicants note that such "unique" or "particular" utilities never have been required by the law.

To meet the utility requirement, the invention must be "practically useful," *Anderson v Natta*, 480 F.2d 1392, 1397 (CCPA 1973) and confer a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534 (1966). The threshold of utility under this standard is not high, and requires merely an "identifiable" benefit. *Juicy Whip Inc.v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999). In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180 (Fed. Cir. 1991), the CAFC explained that "An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

This does not preclude, however, a general utility. Practical real-world uses are ***not*** limited to uses that are unique to a single invention. The law requires that the practical utility be "definite," not particular to only one invention. *Standard Oil Co. v. Montedison,* 664 F.2d 356, 375 (3d Cir. 1981). The courts have not rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention; where courts have found utility to be too "general," it has been in situations when the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a

person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

Inventions that achieve a practical use, a use that is also achieved by other inventions, satisfy the utility requirement. Thus practical utilities can be directed to classes of inventions, so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. *Montedison*, 664 F.2d at 374-75. For example, many materials conduct electricity. This general utility applies to a broad class of inventions (conductive materials) and satisfies the utility requirement of section 101. The fact that other materials also conduct electricity does ***not*** mean that other materials that conduct electricity want for utility. What is important, however, is that ion channels are known to have practical uses. For example, ion channels all have practical uses well beyond throwaway uses like snake food. All of the genes encoding ion channels can be used, for example, for toxicology testing to generate information useful in activities such as drug development, even in cases where little is known as to how a particular ion channel works. No additional experimentation would be required, therefore, to determine whether an ion channel has a practical use as all ion channels have at least one practical use.

The Office appears to be under the impression that inventions that are, *inter alia*, useful for use in research are unpatentable. This is not true. The Patent Office's patent database is replete with patents claiming useful research tools, *e.g.*, spectrophotometers. A material whose only use is as a tool in research may indeed be patentable. *Brenner* and *Kirk* exclude only those research purposes where the ***only*** use of the material itself is as the subject of research. If *Brenner* and *Kirk* had held otherwise, any chemical material would, by virtue of its existence, be useful. However, nowhere do those cases state or imply that a material cannot be patentable if has some other beneficial use in research.

Assay methods, like many other tools used in research, have an immediately realizable "real world" value. For example, an assay method that can identify chemical compounds that possess a particular physical, structural or biological property clearly have "real world" value irrespective and independent from the utility that may be associated with the compounds identified using the assay method. As a consequence, a presumption that assay methods cannot possess utility if the compound isolated or identified using the assay do not have utility would be the product of a flawed analysis of *Brenner*. Such a conclusion also would suggest that processes and products can never possess utility if their utility lies in the field of research. Indeed, the application of this concept of the utility requirement as it relates to methods for assaying or identifying compounds, if taken literally, would mean that claims to methods such as NMR, infrared, x-ray crystallography, and screening for other important biological properties, would be unpatentable because further research would be necessary to establish utility for the compounds identified or assayed. This certainly cannot be the result intended by the Patent Office when issuing these guidelines.

Because all ion channels, as a class, convey practical benefit (much like the class of DNA ligases identified in the Training Materials), there should be no need to provide additional information about them. A person of ordinary skill in the art need not guess whether any given ion channel conveys a practical benefit. Nor is it necessary to know how or why any given ion channel works. It is settled law that how or why any invention works is irrelevant to determining utility under 35 U.S.C. § 101: "[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (quoting *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989).

Applicants need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532. The amount of evidence required to prove utility depends on the facts of each particular case. *In re Jolles*, 628 F.2d 1322, 1326 (CCPA 1980). "The character and amount of evidence may vary, depending on whether the alleged utility appears to accord with or to contravene established scientific principles

and beliefs." *Id.* Unless there is proof of "total incapacity," or there is a "complete absence of data" to support the applicant's assertion of utility, the utility requirement is met. *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992); *Envirotech*, 730 F.2d at 762. The Office has failed to provide proof of "total incapacity", and Applicants have provided information that supports the asserted utilities.

The Office is also reminded that a patent applicant's assertion of utility in the disclosure is presumed to be true and correct. *In re Cortwright*, 165 F.3d at 1356; *Brana*, 51 F.3d at 1566. If such an assertion is made, the Patent Office bears the burden in the first instance to demonstrate that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved. *Id.* To do so, the PTO must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566.

Applicants have demonstrated a "substantial likelihood" of utility by showing a "reasonable correlation" between the utility of the known composition and the composition being claimed. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565 (Fed. Cir. 1996). The presently claimed ion channel is related to known ion channels. The Office has not provided evidence or sound scientific reasoning that one skilled in the art would doubt the "reasonable correlation" advanced by Applicants. Accordingly, under *Brana*, the Patent Office ***must*** accept the utility asserted by Applicants.

Substantial Utility

In addition to conferring a specific benefit on the public, the benefit must also be "substantial". *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA 1980). An asserted utility for a compound that merely invites further research to determine a practical utility is not substantial. In *Brenner*, for example, the U.S. Supreme Court held that a process for making a compound does not confer substantial benefit where the only known use of the

compound was to be the object of further research. *Id.* at 535. Similarly, in *In re Kirk*, the CCPA held that compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 945.

Applicants teach, as described above, that the claimed invention can be used for the production of antibodies; to make hybridization probes and primers to detect nucleic acid molecules that encode the polypeptide of SEQ ID NO:20 and to localize gene expression in tissue samples; to produce a variant or chimeric polypeptide; to create transgenic animals; to detect pharmacogenomically-relevant polymorphisms in individuals; to search for drugs as ligands or antagonists of the claimed polypeptide; and for gene therapy. Thus, it is clear that the claimed invention has real-world uses. All the uses described in the present application are real-world uses and, again, stand in stark contrast to the "throw away" uses (*e.g.*, landfill component or snake food) set forth in the utility guidelines. Thus, there is no question that Applicants have asserted at least one substantial utility and, in fact, have provided numerous substantial utilities. Accordingly, Applicants have complied with the substantial utility requirement.

The Office appears to be under the impression that inventions that are, *inter alia*, useful for use in research are unpatentable. This is not true. The Patent Office's patent database is replete with patents claiming useful research tools, *e.g.*, spectrophotometers. A material whose only use is as a tool in research may indeed be patentable. *Brenner* and *Kirk* exclude only those research purposes where the ***only*** use of the material itself is as the subject of research. If *Brenner* and *Kirk* had held otherwise, any chemical material would, by virtue of its existence, be useful. However, nowhere do those cases state or imply that a material cannot be patentable if has some other beneficial use in research.

Assay methods, like many other tools used in research, have an immediately realizable "real world" value. For example, an assay method that can identify chemical compounds that possess a particular physical, structural or biological property clearly have "real world" value irrespective and independent from the utility that may be associated with the compounds identified using the assay method. As a consequence, a

presumption that assay methods cannot possess utility if the compound isolated or identified using the assay do not have utility would be the product of a flawed analysis of *Brenner*. Such a conclusion also would suggest that processes and products can never possess utility if their utility lies in the field of research. Indeed, the application of this concept of the utility requirement as it relates to methods for assaying or identifying compounds, if taken literally, would mean that claims to methods such as NMR, infrared, x-ray crystallography, and screening for other important biological properties, would be unpatentable because further research would be necessary to establish utility for the compounds identified or assayed. This certainly cannot be the result intended by the Patent Office when issuing these guidelines.

The claimed invention in *Brenner* was directed to a method whose ***only*** utility was making a class of steroids. The disclosure in Brenner failed to disclose a utility for the products of that method, which in turn led to a § 101 rejection because the products resulting from the method lacked utility. The Applicant admitted that the products produced by the method would not be patentable if they lacked utility. 148 USPQ 696. The Court stated that the method lacked utility as well, holding:

> We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product.

148 USPQ 696.

In *Brenner*, the method of making the compounds, which was the only use recited, was inextricably bound up with the compounds themselves and, as a result, the requirement for utility could not be met until a use for the compounds was found. The Court emphasized that the utility of the claimed invention (i.e., the products) would require further research to identify and ascertain, and the compounds produced by the method would be the objects of that research.

In contrast, ion channels related to known ion channels stand on a very different basis. As discussed, there are a multitude of utilities for the claimed polypeptides, including their ability to facilitate research.

The Claimed Invention Has A Credible Utility

In addition to a specific and substantial utility, the Utility Examination Guidelines require that such utility be "credible" (a "credible utility"). That is, whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. Clearly, the numerous specific and substantial utilities asserted by Applicants are credible. Assertions of credibility are credible unless "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion." (See, Revised Interim Utility Guidelines Training Materials.) Further, the PTO is reminded that it must treat as true a statement of fact made by Applicants in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. All the utilities described for the antibodies and polypeptides are based on sound logic. The Office has provided no evidence that the logic is seriously flawed or that the facts upon which these assertions are based are inconsistent with the logic underlying the assertions.

The Examiner cites literature allegedly identifying difficulties that ***may*** be involved in predicting protein function. None of the cited references, however, suggests that functional homology cannot be inferred by a reasonable probability in any particular case. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over many amino acid residues is exceedingly small. Brenner et al., *Proc. Natl. Acad. Sci.* **95**:6073-78 (1998) (See, attached reference).

In the present application the claimed polypeptides are related to the 2 P domain potassium receptor. As set forth on pages 80-81, this relationship was determined:

> using the known protein sequences of ion channels from the SWISSPROT database as query sequences to find patterns suggestive of novel ion channels . . . Positive hits were further analyzed with the program BLASTX against the non-redundant protein and nucleotide databases maintained at NCBI to determine which hits were most likely to encode novel ion channels, using the standard (default) parameters.

The probability, therefore, that the claimed polypeptides' function and structure are related to those of the 2 P domain potassium receptor is, accordingly, very high. The

Office has failed to provide any "countervailing evidence" required by the Utility Examination Guidelines to show that the relationship does not exist. Therefore, no countervailing evidence that says the present invention does not have a substantial, credible, and useful invention has been provided.

Furthermore, ion channel proteins have a well-established utility. Many medically significant biological processes mediated by signal transduction pathways involving ion channels are recognized as important therapeutic targets for a wide range of diseases. In this respect, the ion channel family is analogous to the chemical genus that was the subject of *In re Folkers*, 145 USPQ 390 (CCPA 1965) (Compound that belongs to class of compounds, members of which are recognized as useful, is considered useful under §101.) The Patent Office does not serve the public by attempting to substitute a formulaic analysis of § 101 for the established judgment of the biopharmaceutical industry as to what is "useful." If the Patent Office is aware of any well-grounded scientific literature suggesting that ion channels are not useful, Applicants request that it be made of record.

Art-Recognized Utility

The Utility requirement may also be satisfied by an "Art Established Utility" which means that "a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention... and the utility is specific, substantial and credible." (M.P.E.P. §2107).

The Revised Guidelines state that a Patent Examiner should not reject an application for lack of utility if the asserted utility "would be considered specific, substantial, and credible by a person of ordinary skill in the art ***in view of all of the evidence of record***." Revised Guidelines at ¶ 4 (emphasis added).

There is no restriction on the kinds of evidence an Examiner may consider in determining whether a "real-world" utility exists. Indeed, "real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate

conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856 (6th Cir. 1932).

Applicants further assert that long held pre-Brenner case law standard supports judging the utility of an invention on whether or not the public derives a benefit from the invention, regardless of how slight the benefit. *See,* for example, *In re Nelson*, 280 F.2d 172, 178-180 (C.C.P.A. 1960) (stating that "however slight the advantage which the public have received from the inventor, it offers a sufficient reason for his compensation") (citing ROBINSON ON PATENTS (1890)); *see also Lowell v. Lewis*, 1 Mason 182 (Fed. Case. No. 8568, 1817) (stating "if it be more or less useful is... of no importance to the public. If it be not extensively useful it will silently sink into contempt and disregard"). Polypeptides of all types are broadly used in the biotechnology industry, playing key roles in drug and disease discovery processes. Indeed, many such fragments enable researchers to find the genes associated with physiological functions. The discovery of such functions readily benefits the public. Accordingly, such tools could satisfy the pre-Brenner case law standard.

Applicants note for the record that the Patent Office has issued patents in the filed of ion channels for applications disclosing the same amount of information as is described in the present application. The Office has granted and apparently continues to grant patents to ion channel proteins, their encoding polynucleotides and antibodies directed to them ***in which no specific biological activity has been confirmed.*** Specifically, Applicants would like to bring the following US Patents to the Office's attention:

6,562,593 Merkulov et al. "Isolated human transporter proteins, nucleic acid molecules encoding human transporter proteins, and uses thereof" (Claims an isolated polynucleotide and method for producing polypeptide)
6,503,733 Bandman et al. "Human anion channel" (Claims an isolated polynucleotide, an isolated polypeptide and an antibody that binds to the polypeptide)
6,228,616 Bandman et al. "Human anion channel" (Claims a purified antibody)
5,854,411 Goli et al. "Human Chloride Channel" (Claims an isolated polynucleotide)
6,451,554 Wood et al. "Ion Channel" (Claims an isolated polynucleotide and a method of producing a polypeptide encoded by the polynucleotide.)

6,309,858 Dietrich et al. "T-type calcium channel variants; compositions thereof; and uses" (Claims an isolated polynucleotide).
6,309,855 Duprat et al. "Family of mammalian potassium channels, their cloning and their use, especially for the screening of drugs" (Claims isolated polynucleotide)
6,207,410 Hall et al. "Genes encoding an insect calcium channel" (Claims isolated polynucleotide and methods)
6,087,488 Ganetzky et al. "Potassium ion channel genes and proteins" (Claims isolated polynucleotide)
6,013,474 Ellis et al. "Calcium channel compositions and methods" (Claims isolated polynucleotide)
5,710,019 Li et al. "Human potassium channel 1 and 2 proteins" (Claims an isolated polypeptide)

Applicants submit that these issued US Patents are evidence of an art recognized utility for ion channels whose natural function or association with disease is unproven. Upon review of the file histories of several of the above-identified patents, it is apparent that the present application provides at least as much functional data as the applications giving rise to the issued patents provided. For example, U.S. Patent 6,562,593 is directed to:

> An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:
> (a) a nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO:2;
> (b) a nucleotide sequence consisting of the nucleic acid sequence of SEQ ID No:1; and
> (c) a nucleotide sequence that is completely complementary to a nucleotide sequence of (a)-(b).

(claim 1). The specification of the patent reveals that the claimed sequences were "related to the differentiation-associated Na-dependent inorganic phosphate cotransporter subfamily." (*see* column 11, lines 34-55) . Based on this disclosure it is assumed that the physiological role of the claimed channel is in the transport of inorganic phosphate. The specification further provides sequence information, and the putative identification of structural elements including start codon, stop codon, and phosphorylation sites (*see* Figure 1).

The present application provides analogous information to that set forth by U.S. Patent 6,562,593. For example, a putative function for the claimed invention is set forth

on page 34 of the instant application that states that the invention is related to the 2 P domain potassium receptor. Based on this disclosure, the channel is assumed to be a potassium receptor (for example, a TASK-2 receptor). As set forth in Reyes et al. (J Biol Chem, Vol. 273, Issue 47, 30863-30869, November 20, 1998; copy attached hereto), the properties of 2P domain K^+ channels suggest that they are involved in the generation and the modulation of the resting potential of many cell types. Sequence information relating to the claimed polypeptides is included throughout the specification and the appended sequence listing. Using search utilities well known to those skilled in the art at the time the present application was filed and methods described in the application, the skilled artisan can readily determine phosphorylation sites and localization of expression.

Furthermore, Applicants point out that commercial products relating to ion channel polypeptides for which no function has been confirmed are available. For example, a brief review of available antibodies reveals several anti-TASK-2 antibodies (which, as discussed above, are 2 P domain potassium receptors) (*see* attached product sheets). The fact that companies make and sell such products proves that there is a well-established utility for the presently claimed polypeptides. Accordingly there could be no better proof of the utilities of the claimed polypeptides- such products are made by a manufacturer (who expects to sell them) for consumers (who expect to buy them). Any argument that there is no art-recognized utility for such ion channel polypeptides seems meritless.

Antibodies

The Examiner notes that "antibodies can be made to any polypeptide . . .[but] . . . if the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility." (Office Action, page 5).

Applicants respectfully assert that the specific amino acid sequence of SEQ ID NO:20 set forth in the application is a specific and substantial disclosure for the utility of antibody production. An antibody specific for SEQ ID NO:20 would, by definition, not bind to another polypeptide. As set forth on page 34, the claimed polypeptide is related to

the 2 P domain potassium receptor. Accordingly, antibodies against the claimed polypeptide would be useful, *inter alia*, in differentially identifying the claimed polypeptide from other 2 P domain polypeptides. Such a utility is not a "throw away" use. As discussed above, the fact that other ion channels that transport potassium are known does not mean that further materials that ion channels that transport potassium want for utility. What is important, is that ion channels are known to have practical uses.

Detection of nucleic acid molecules and localization of gene expression

The Office alleges that "probes and primers can be designed from any polynucleotide sequence. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial."

Applicants respectfully assert that SEQ ID NO:1 represents the nucleotide sequence corresponding to SEQ ID NO:20. SEQ ID NO:1 represents a specific target for primers and probes for detection of nucleic acid molecules and for localization of gene expression. As discussed above, the claimed polypeptide is related to the 2 P domain potassium receptor. Accordingly, such primers and probes for SEQ ID NO:1 or SEQ ID NO:20 would be useful, *inter alia*, in differentially detecting the nucleic acid molecules encoding the claimed polypeptide from nucleic acid molecules encoding other 2 P domain polypeptides. Such a utility is not a "throw away" use.

Production of variant or chimeric polypeptide

The Office alleges that the utility asserted "can be performed with any polypeptide or polynucleotide encoding a polypeptide. Further, the specification discloses the specification discloses nothing specific and substantial for the variant polypeptide that is produced by this method."

Applicants respectfully assert that the specific amino acid sequence of SEQ ID NO:20 set forth in the application is a specific and substantial disclosure for the utility of producing a variant or chimeric polypeptide. A variant or chimera of SEQ ID NO:20

would, by definition, be specific to SEQ ID NO:20. Examples of the generation of chimeric receptors are set forth, *inter alia*, in Example 11. Such a utility is not a "throw away" use. Again, the fact that other ion channels that transport potassium are known does not mean that further materials that ion channels that transport potassium want for utility.

Creation of transgenic animals

The Office asserts that "the specification does not disclose a phenotype associated with a mutated, deleted, or translocated gene encoding the present invention . . . or what specific tissues and cells are being targeted."

Applicants respectfully assert that the specific amino acid sequence of SEQ ID NO:20 set forth in the application is a specific and substantial disclosure for the utility of creating transgenic animals. Other asserted utilities set forth herein can be employed without serious burden to determine, *inter* alia, the specific tissues and cells targeted. Such a utility is not a "throw away" use.

Detection of pharmacogenomically-relevant polymorphisms

The Office alleges that Applicants have not "demonstrated the function of the claimed polypeptide . . . much less clinically-relevant polymorphisms." Further the Office alleges that "many unrelated sequences can be polymorphic, generally."

Applicants respectfully assert that the function of the claimed polypeptide has been identified in the present application. As noted throughout the specification, Applicants teach that the polypeptide encoded by SEQ ID NO:20 is an ion channel. Also, as discussed above, the claimed polypeptide is related to the 2 P domain potassium receptor. The disclosure of the amino acid sequence of this ion channel is a specific and substantial disclosure, in this instance for detecting polymorphisms in the ion channel. The opinion that "many unrelated sequences can be polymorphic" is unavailing; a polymorphism in an ion channel encoded for by SEQ ID NO:20 is specific to SEQ ID NO:20. Such a utility is not a "throw away" use.

To search for drugs as ligands or antagonists

The Office alleges that Applicants have not "characterized the claimed polypeptide of SEQ ID NO:20." Further the Office alleges that "there is no disclosure of how to assay for ligand binding . . ."

Applicants respectfully point out that characterization of the claimed polypeptide is not necessary to support an asserted utility. Notwithstanding this, Applicants again point out that the claimed polypeptide has been characterized as an ion channel. Further, as noted on page 34 of the application as filed, the claimed ion channel is related to the 2 P domain potassium receptor. Contrary to the Office's assertion, the present application has ample disclosure of assays for ligand binding. For example, pages 47-52 provide such assay information and incorporate several references by reference which detail such assays. Further, each of Examples 7-10 set forth assays to measure ligand binding. Such a utility is not a "throw away" use. Further, ligands and/or antagonists of the ion channel encoded by SEQ ID NO:20 are specific to SEQ ID NO:20. Indeed, the Examiner has failed to provide any evidence that an antagonist or ligand of the claimed invention would also be an antagonist or ligand of other 2 P domain potassium receptors.

Gene therapy

The Office alleges that the utility asserted "can be performed for any polynucleotide. Further, the specification does not disclose diseases associated with a mutated, deleted, or translocated gene encoding the claimed invention. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial."

Applicants respectfully assert that the specification does disclose diseases associated with aberrant expression of ion channels. The disclosure of the amino acid sequence of this ion channel is a specific and substantial disclosure, in this instance for detecting performing gene therapy. Such a utility is not a "throw away" use.

Credible and specific, but not substantial

Ion channels

The Office acknowledges that the asserted utility of the present invention is credible and specific, but alleges that the utility is not substantial. Specifically, the Office alleges that "members of this large family of proteins share several recognizable structural similarities, yet have diverse functions." Further, the Office alleges that "the specification does not disclose characteristics specific to a voltage-gated channel (e.g. Nernst potential, conductance, reversal potential, ion selectivity, etc), any blockers, its physiological role in the organism, or a link between the channel and a specific condition or disease state. Determination of any of these would require significant further research. Since the asserted utility is not available as a real world utility, and significant further research beyond the disclosure is required, the asserted utility is not substantial. "

Applicants respectfully point out that although, as correctly pointed out by the Office, that the claimed polypeptide is a member of a large family of proteins (ion channel family), the present application also teaches that the claimed polypeptide is also a member of a smaller family within the ion channel family. As noted on page 34 of the application as filed, the claimed ion channel is related to the 2 P domain potassium receptor (TASK-2). As such, the functions of the claimed ion channel are not as diverse as would be true if the claimed ion channel was only characterized as an ion channel polypeptide, or even as a potassium channel. However, the functions of a member of the 2 P domain potassium receptor family member are much less diverse. With regard to specific electrochemical characteristics of the claimed ion channel, Applicants have already taught that the channel is a potassium channel. Applicants respectfully assert that further characteristics of the ion channel are not required to prove utility. However, in an effort to advance the prosecution of the present application, Applicants respectfully assert that that functional characteristics of the 2 P domain potassium receptor family members are known to the art skilled. (*See*, for example, Reyes et al., which describe the characteristics of 2 P domain potassium (TASK-2) receptors.)

Applicants have asserted utilities that are specific, substantial and credible, and well established. Accordingly, the Utility Requirement has been satisfied. Applicants therefore respectfully request the withdrawal of the rejection under 35 U.S.C. § 101.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 30-35, 74, 75 and 89-94 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to adequately teach how to use the instant invention. According to the Office, "since the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well established utility...one skilled in the art clearly would not know how to used the claimed invention." (Office Action, page 8) Applicants respectfully disagree.

As discussed above, the present invention ***is*** supported by a specific, substantial, and credible asserted utility as well as a well-established utility. Accordingly, Applicants respectfully request that the rejection be withdrawn.

The Office alleges that the specification "does not teach functional or structural characteristics of the polypeptide or polynucleotide recited in the claims." (Office Action, page 8). Further, the Office cites references that are said to provide evidence that "function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." (Office Action, page 9). Applicants respectfully disagree with the Office's characterization of the cited references.

For example, Scolnick *et al.* does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Instead, Scolnick states that "the sequence-to-function approach is the most commonly used function-prediction method. This robust filed is well developed . . ." Although Scolnick acknowledges that there are limitations to sequence-based approaches, Scolnick indicates that "for proteins whose sequence identity is above ~30%, one can use homology modeling . . ." Further, Scolnick states that even if inexact models (of protein structure) are used, based on homology, "structure from sequence can be used for the subsequent prediction of biochemical function." (Scolnick, page 35).

Similarly, Doerks does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Doerks discusses faulty characterization of UPFs (uncharacterized protein families). By definition UPFs contain members in at least 3 taxonomically and phylogenetically distinct species and do not contain biochemically characterized proteins. Using, *inter alia*, sequence homology, Doerks was able to provide functional annotation for "more than 700 of the 1300 proteins clustered in 25 of the 58 distinct UPFs. . . . , for another 13 UPFs currently containing about 250 proteins, the presence of transmembrane regions was recorded. *Id.*" (Doerks, page 250). Although Doerks acknowledges that there are pitfalls to be avoided in annotating protein sequences, the fact that Doerks was able to ascribe a function to more than 700 out of 1300 proteins and to identify structural elements in another 250 proteins indicates that function can be predicted based on sequence similarity.

Smith does not say that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Instead, Smith states that "the major problems associated with nearly all the current automated annotation approaches are- paradoxically – minor database annotation inconsistencies (and a few outright errors). (Smith, page 1222).

Brenner discusses "Errors in genome annotation". Although Brenner alleges that there are problems with inferring function from homology, the data presented does not support the Office's position that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and instead supports the use of sequence-function prediction. Indeed, on reviewing Table 1 on page 133, it appears that the highest "minimum error rate" in annotating genes was calculated to be 15%. If this is to be believed, it must be assumed then that at most, 85% of the annotations were correct.

The Office cites Lehmann-Horn as evidence that function prediction is problematic. Specifically, the Office alleges that Lehmann-Horn "shows that members of a class do not always share a specific and substantial functional attribute or utility, despite having structural features in common." (Office Action, page 10). However, Applicants were unable to find support for the Office's assertion at the cited location.

Instead, what Lehmann-Horn does state is that "because of the high variability in structure [between different potassium channels], the channels can be classified according to the number of pore regions (P) and the number of helical structures that were thought to correspond to the number of transmembrane segments (termed T or S in the voltage-gated and M in the 4 ligand-gated channels)." (Lehmann-Horn, pages 1329-1330). So, although there may be variability among families of potassium channels, receptors ***can*** be classified based on other features, including number of pores. As discussed above, the present invention is related to a 2 Pore potassium channel. Accordingly, the alleged variability may be relevant to potassium channels in different families, but the cited reference does not say that there is significant variability within specific sub-families, e.g. 2 pore potassium channels.

The Office also alleges that the application fails to teach "how to use the claimed ion channel-like polypeptide for any purpose." (Office Action, page 10). As discussed above, Applicants have taught several specific, substantial and credible utilities for the claimed invention. Further, the specification as filed teaches the art-skilled how to use the claimed invention. For example, the specification teaches how to use the claimed invention in the Interaction Trap/Two-Hybrid System (Example 7); in FRET Analysis of Protein-Protein Interactions Involving Ion Channel Polypeptides (Example 8); in Assays to Identify Modulators of Ion Channel Activity (Example 9); in High throughput screening for modulators of ion channels using FLIPR (Example 10); and as Chimeric Receptors (Example 11).

The Office also alleges that a "large amount of experimentation [would] be necessary to determine an activity of property of the claimed polypeptide . . ." (Office Action, page 11). However, the Office has failed to provide any substantive evidence that using the claimed invention would require undue experimentation. Applicants respectfully assert that any experimentation required would be routine. Moreover, even voluminous research is not undue so long as it is of a routine nature. *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Pat. Off. Bd. App. 1986).

The Office alleges that the specification "does not reasonably provide enablement for use of an allelic variant as recited in claims 34 and 93. . . [c]laims 34 and 93 encompass numerous undefined variants of SEQ ID NO:1." (Office Action, page 11). Applicants disagree.

Notwithstanding the foregoing, claim 34 was canceled without prejudice and claim 93 is assumed to have been withdrawn from consideration, rendering the rejection, to the extent it applies to claims 34 and 93, moot.

Claims 74 and 75 were rejected for their recitation of a "chimeric receptor." Although Applicants disagree, claims 74 and 75 have been cancelled without prejudice.

Claims 34, 74, 75, and 93 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to provide written description for the claimed subject matter. Although Applicants disagree and assert that ample written description for claims 34, 74, 75, and 93 exists in the specification as filed, claims 34, 74 and 75 were canceled without prejudice. As discussed above, it is assumed that claim 93 was withdrawn from consideration.

In view of the foregoing, Applicants respectfully request that the rejection of claims 30-35, 74, 75 and 89-94 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 32, 33, and 92 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office alleges that the term "homologous" and the phrase "at least one conservative amino acid substitution", encompass "many unknown proteins." (Office Action, page 14). Applicants respectfully disagree.

Applicants note that as discussed above, it is assumed that claim 92 was removed from consideration. Claims 32 and 33 were amended to recite a specific level of homology and to remove the phrase "at least one conservative amino acid substitution"

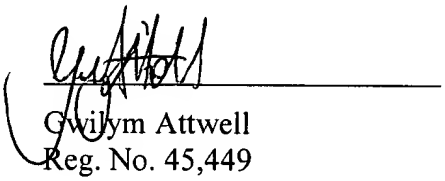
from claim 33. Applicants respectfully assert that the pending claims are clear and definite.

In view of the foregoing, Applicants respectfully request that the rejection of claims 32, 33, and 92 under 35 U.S.C. § 112, second paragraph, be withdrawn.

Conclusion

Applicants believe the claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,



Gwilym Attwell
Reg. No. 45,449

Date: November 3, 2003
COZEN O'CONNOR, P.C.
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-2000
Facsimile: (215) 665-2013

Attachments: Reyes et al. (J Biol Chem, Vol. 273, Issue 47, 30863-30869, November 20, 1998)
Brenner et al. (Proc. Natl. Acad. Sci. **95**:6073-78, 1998)
US Biological Product Sheet
Alomone Labs Product Sheet
Sigma-Aldrich Product Sheet